

iFORUM

NEWS AND VIEWS

Should We Be Trying to Define Responders to Cardiac Resynchronization Therapy?

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CARDIAC RESYNCHRONIZATION THERAPY (CRT) MAY PROVIDE A DRAMATIC IMPROVEMENT of symptom status and outcome in many patients with heart failure. Unfortunately, the use of current selection criteria is associated with a failure to respond on symptomatic or functional grounds of approximately 30%. Does the falling implant rate reflect a lack of enthusiasm for a treatment whose efficacy is not guaranteed—despite the certainty of risk and cost—or does it reflect the inappropriate application of other criteria of mechanical synchrony? The accompanying positions encapsulate the arguments of skeptics and supporters of the role of mechanical dyssynchrony.

Cleland et al. point out a number of conceptual areas in the mechanical synchrony hypothesis that are problematic. The definition of “response” is itself fraught in an evolving illness, the role of mechanical synchrony in patient selection is unproven, the currently used imaging markers seem to have both a limited predictive ability and low reproducibility, and the evidence of benefit from device optimization is limited. These authors conclude that there may be some room for selection—some patients are too well and others too sick to benefit from CRT—but that N-terminal pro-B-type natriuretic peptide (NT-proBNP) may be the most useful tool for selection.

Although the mechanical indexes have been insufficiently studied in a randomized trial design, Gorcsan argues that there is a strong evidence base relating to the efficacy of mechanical markers for the prediction of left ventricular (LV) recovery, and emphasizes the shortcomings of the multicenter PROSPECT (Predictors of Response to CRT) study, which is often cited as evidence against the role of mechanical

synchrony. This section also stresses that the assessment of synchrony is not the only marker of LV response to CRT, with important roles for scar burden, lead placement, and advanced heart failure. The truly remarkable aspect of this Viewpoint report is the congruity between the discussants on the important topics, especially the contribution of nonsynchrony features to “responsiveness.”

Try, of Course, but Do Not Apply Theories That May Be Wrong and Detrimental to Patient Care!

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WHAT DOES IT MEAN TO RESPOND TO A THERAPY? It does not just mean to have a good outcome with an intervention, since this

would imply that all healthy people should be treated with it, because they are likely to have a good outcome even if the treatment is bad (1). To respond to a therapy means that the patient does better with the treatment than without it. In other words, treatment alters symptoms and/or outcome. Some patients who respond will still have a bad outcome, and some patients who do not respond will have a good outcome. There are those too well to respond and those too sick to respond, but these nonresponders will have very different outcomes. The art of medicine is to use knowledge both of outcome and response to choose a therapy for an individual patient. Observational studies can help gauge the likely outcome for a patient who receives a therapy but can be confounded by misconceptions about the patient's prognosis without the therapy. Randomized controlled trials (RCTs) are required to address the issue of response. Even in the context of a RCT, it may be difficult to tell if an individual patient has responded. RCTs are designed to look at group effects. If the study is large enough, it may have the statistical power to look at response in subgroups but it still requires an act of faith to apply this to an individual patient.

Having grappled with the concepts of outcome and response, it is now necessary to define them in concrete terms that can be applied to the clinical setting. A binary classification of response is too simplistic for CRT. The spectrum of response to CRT will vary from deterioration, through no discernable improvement, to small, medium, and large gains. This classification will be highly dependent on the outcome chosen and the threshold of effect used to define response. Small differences in the definition can

make huge changes in response rates (2). From a patient's perspective, improvement in symptoms is the clearest evidence of response, although the reasons for improvement are often multifactorial, including the intervention in question, adjustment of concomitant medication, or simply relief on the patients' part that a major intervention has taken place and they have not been damaged by it! Not getting worse and not dying are clearly highly desirable goals for most patients but the absence of a problem already starts to become a statistical issue rather than a purely clinical one because the patient and clinician do not really know whether the patient would not have deteriorated within that time frame even without the intervention. Measurements made by a doctor are an even less certain measure of response, as they depend on the faith of the doctor that the change in measurement is a good surrogate for outcome. Clearly, improvements in cardiac function are grounds for optimism; experience with inotropic and many other failed interventions for heart failure shows that basing therapy on hypothetical mechanisms of benefit is not a reliable measure of clinical success (3). For instance, in the CARE-HF (Cardiac Resynchronization–Heart Failure) study, patients with ischemic heart disease had a worse prognosis regardless of which treatment they were assigned to (4) and a substantially smaller improvement in left ventricular ejection fraction (5), but had a somewhat greater reduction in mortality if assigned to CRT rather than to the control group (6). Thus, patients with ischemic heart disease had a poorer outcome and a poorer echocardiographic response, but a greater clinical response to CRT.

To summarize these arguments, randomized controlled trials of ade-

quate size and duration with clinically relevant outcomes, including symptoms and prognosis, are required to assess the likelihood of response to therapy, overall and in subgroups. The larger trials have shown remarkably consistent benefit, although some did not attain significance on their primary end point (5–11). Subgroup analysis of the 2 largest trials that investigated patients with moderate or severe heart failure, the CARE-HF study and the COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure) study, identified little heterogeneity across subgroups, especially with harder outcomes like death as opposed to the softer primary outcome measure of all-cause hospitalization or death. A detailed analysis of the CARE-HF study (11), including the 3-month echocardiographic response to CRT, failed to identify any useful markers of response although several powerful markers of outcome, including plasma concentration of NT-proBNP and the severity of mitral regurgitation, were identified. These data could be used clinically to identify a group of patients so well that they do not need CRT and another group who are so sick that implanting a CRT device, although it might be associated with a good response, might still be associated with a poor outcome.

Another greater confounder of responder-analyses is time. Heart failure is a progressive disease that is constantly mutating and evolving—just like many other malignant diseases. Disease progression is also heterogeneous, and its rate and pattern of progression reflects the underlying disease modified by the effects of therapy and punctuated by sudden arrhythmic or vascular death. Progressive remodeling and increases in PR and QRS inter-

vals are seen (12) (Fig. 1). Dyssynchrony is not a fixed problem (13); changes with stress and with disease progression may be the final “nail in the coffin” to trying to select patients based on evanescent images. The REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) study, which enrolled patients with mild or no symptoms, suggested that patients with QRS interval <152 ms or who did not require diuretic therapy were less likely to have worsening heart failure prevented by CRT in the first 12 months (7), a finding that probably reflects the low risk of deterioration and the modest length of follow-up in this group. By 24 months, these differences had vanished. In the CARE-HF trial, benefits that were modest at 1 year were striking by 3 years, whether the outcome was hospitalization or death from worsening heart failure or sudden death (5,14).

What is the evidence that ventricular dyssynchrony can be used to select patients for CRT? In fact, it is more the absence of evidence that supports any sort of argument for case selection by the severity of ventricular dyssynchrony. The CARE-HF study excluded patients with an interventricular mechanical delay (IVMD) <40 ms if their QRS width was <150 ms. None of the other major trials of CRT required any evidence of ventricular dyssynchrony other than prolonged QRS width. Both the MIRACLE (Multicenter InSync Randomized Clinical Evaluation) study and the CARE-HF trial show that patients with more IVMD have a better prognosis in both the control and the CRT groups (15,16) (Fig. 2). In other words, all observational trials should show that patients with more IVMD do better. However, this reflects the natural history of disease and cannot be taken as evidence of a response to

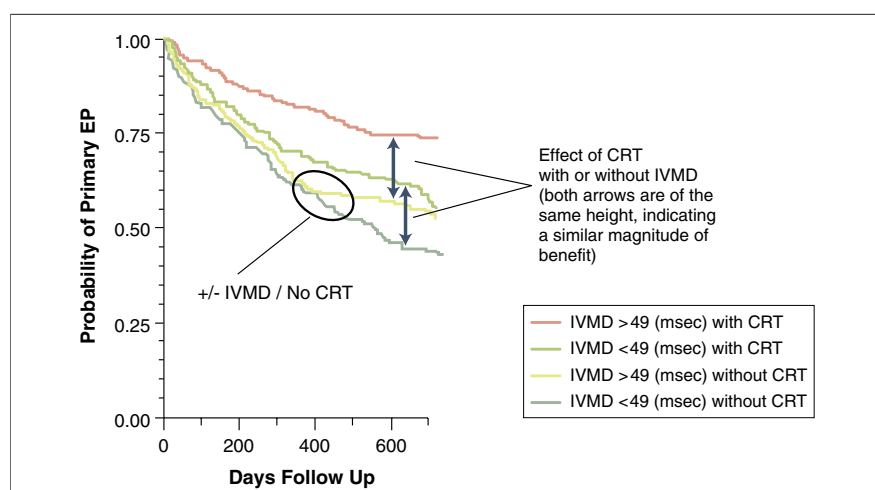


Figure 1. Probability of Death or Unplanned Admission to Hospital for Major Cardiovascular Event

Patients with interventricular mechanical delay (IVMD) >49 ms fared significantly better whether or not they received cardiac resynchronization therapy (CRT). For each 10 ms increase in IVMD, the hazard ratio (HR) for all-cause mortality was 0.87 (95% confidence interval: 0.83 to 0.92) and was an independent marker of a good prognosis in a multivariable model. Red line indicates IVMD >49 ms with CRT; green line indicates IVMD <49 ms with CRT; yellow line indicates IVMD >49 ms without CRT; and gray line indicates IVMD <49 ms without CRT.

therapy. It is logical that, when the left ventricular ejection fraction (LVEF) is depressed, dyssynchrony is a good thing to have. It indicates more viable myocardium. If the dyssynchrony suddenly vanishes, as might happen with CRT, the LVEF may instantaneously increase by 5% to 10%, which might be a good thing but is no guarantee of clinical success. Conversely, if the LVEF is 30% and there is no dyssynchrony then the LVEF really is 30%.

There is a bewildering array of measures of dyssynchrony (17). Their reproducibility and predictive power for response and outcome is low.

The intelligent reader, by this time, should be wondering whether the effect of CRT is mediated by correcting ventricular dyssynchrony. The conclusion of those who trouble themselves to try and optimize programming after implantation is—“probably not.” Substantial RCTs of ventricular pro-

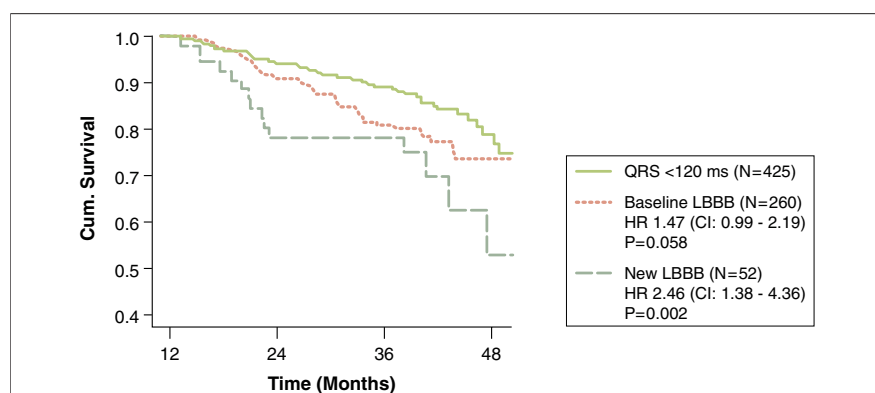


Figure 2. Prognostic Significance of Chronic and New-Onset LBBB

Green line indicates QRS <120 ms; orange line indicates baseline left bundle branch block (LBBB); gray line indicates new LBBB. Cum. = cumulative; HR = hazard ratio.

gramming after CRT have failed to show an important effect of sequential versus simultaneous right and left ventricular pacing (18,19). If dyssynchrony is so heterogeneous, then why is there so little benefit from trying to personalize the ventricular pacing interval? There are no substantial outcome trials of atrioventricular (AV) pacing. One of the better markers of benefit with CRT (although still weak) is blood pressure (20). Patients with a systolic blood pressure <120 mm Hg did badly in the control groups of these studies but did much better if they received CRT. One of the most consistent effects of CRT in patients with advanced heart failure is a rise in systolic blood pressure—7 mm Hg on average in both the COMPANION study and the CARE-HF study, which means that some patients had 10 to 15 mm Hg increases. Optimizing the AV pacing interval has far more powerful effects on blood pressure than optimizing the ventricular (VV) interval (20). Interestingly, the PR interval was a better predictor of outcome than QRS duration or bundle-branch block pattern in the CARE-HF study (21), and patients with PR interval <150 ms were excluded from the COMPANION study. In summary, it may be that most of the benefit of CRT reflects optimization of the AV interval, with the caveat that intervention that makes ventricular dyssynchrony worse (i.e., right ventricular pacing) should be avoided. Even this may not be true. No adequate study of AV optimization with univentricular pacing has been conducted. Early studies may just not have been long enough or large enough (22,23).

Is there any evidence that might support an argument for ventricular dyssynchrony being an important substrate for the effect of CRT? Not

much. Observations do suggest that the site of left ventricular pacing is important, and this is most easily explained by an effect on ventricular dyssynchrony. It may not be important in all patients, and it is possible that it reflects timely activation of relatively small but important regions such as the papillary muscles. The decline in mitral regurgitation is often abrupt when CRT is switched on and associated with an increase in systolic blood pressure (7). Perhaps we should pay more attention to the amount and nature of mitral regurgitation and to AV dyssynchrony and less to the QRS interval and the ventricle when selecting patients for CRT.

There is little evidence that QRS width is any better at predicting benefit than echocardiographic dyssynchrony. Use of QRS width may be confounded by the bundle branch block pattern. The main report of the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial—Cardiac Resynchronization Therapy) study suggested that QRS width predicted the benefit in terms of less worsening heart failure in patients assigned to CRT, but further analysis suggested the left bundle branch block (LBBB) pattern was a much better predictor, regardless of QRS width (24). However, in the CARE-HF and MIRACLE studies, patients with right bundle branch block (RBBB) and LBBB obtained similar benefits from CRT regardless of QRS duration (25), although patients with RBBB had a poorer outcome regardless of assigned therapy, which confounds observational analyses. As noted above, QRS duration gets progressively longer with follow-up. Moreover, during periods of decompensation there appears to be a reversible prolongation of QRS duration

in many patients (35). In heart failure, QRS duration varies.

Another problem is the nature of the expected benefit from CRT. The received wisdom is that CRT improves cardiac function leading to an improvement in symptoms and prognosis, with the latter achieved primarily by reducing death due to worsening heart failure. However, just because these things are associated does not mean that they are cause and effect. CRT alone reduces sudden death, and there is no evidence that CRT with defibrillator (CRT-D) exerts a greater effect on all-cause mortality (26). The reduction in sudden death may just reflect a reduced arrhythmic substrate due to improved cardiac function. However, numerous reports suggest that many sudden deaths in patients with heart failure are due to bradyarrhythmias which might be prevented simply by the pacing function of CRT (27).

When deciding to use an angiotensin-converting enzyme inhibitor or beta-blocker for heart failure, clinicians use the entry criteria for the respective clinical trials, using the criteria as a rough guide to which patients are likely to benefit rather than as a strict set of rules. The idea that patients with a LVEF of 39% will benefit and those with 41% will not is highly improbable. It is also possible that there are no useful criteria by which to select patients for CRT other than by extremes of clinical risk. Some patients will be clearly too well to benefit and others too sick. NT-proBNP, rather than echocardiography, might be the most useful tool in this respect (28) (Fig. 3). Currently, the only scientific grounds for withholding CRT in patients with a narrow QRS width, less severe ventricular dysfunction, or in atrial fibrillation is an absence of adequate trial evi-

dence. We need to dare to fail in order to succeed. Perhaps all patients with high-risk heart failure, readily assessed with a simple blood test, should have a device implanted. This could be used to monitor the disease, to improve ventricular function immediately or in the future, and to prevent sudden death.

Improving Patient Selection for CRT Will Improve Patient Outcomes

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CRT IS UNDOUBTEDLY ONE OF THE MOST BENEFICIAL NEW THERAPIES FOR HEART FAILURE patients in the past 10 years (9–11). The dramatic improvements that may result from CRT in patient's quality of life and survival are undisputed. Presently, patients are recommended for CRT for severe symptomatic heart failure, depressed LVEF, and electrocardiographic QRS widening ≥ 120 ms. The disappointing and frustrating phenomenon is that a significant proportion of patients who receive this therapy by current selection guidelines do not seem to benefit from or respond to CRT. The proportion of nonresponse ranges from approximately 25% to 35%, depending on whether one uses a definition of clinical symptomatic response or a more objective LV reverse remodeling response (17). Nonetheless, there is an important incentive to improve patient selection because CRT implantations are associated with rare, but potentially serious, complications including coronary sinus dissection and death (29). Sanderson (30) in a recent commentary argued eloquently that attempting to identify nonresponders to CRT is extremely worth-

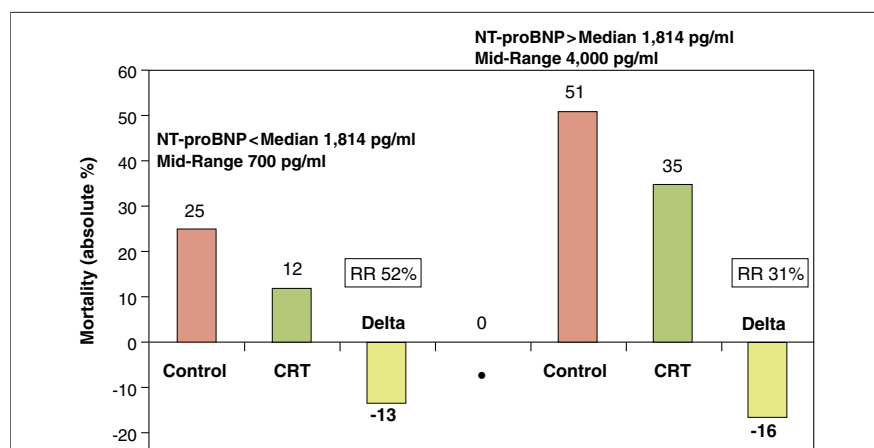


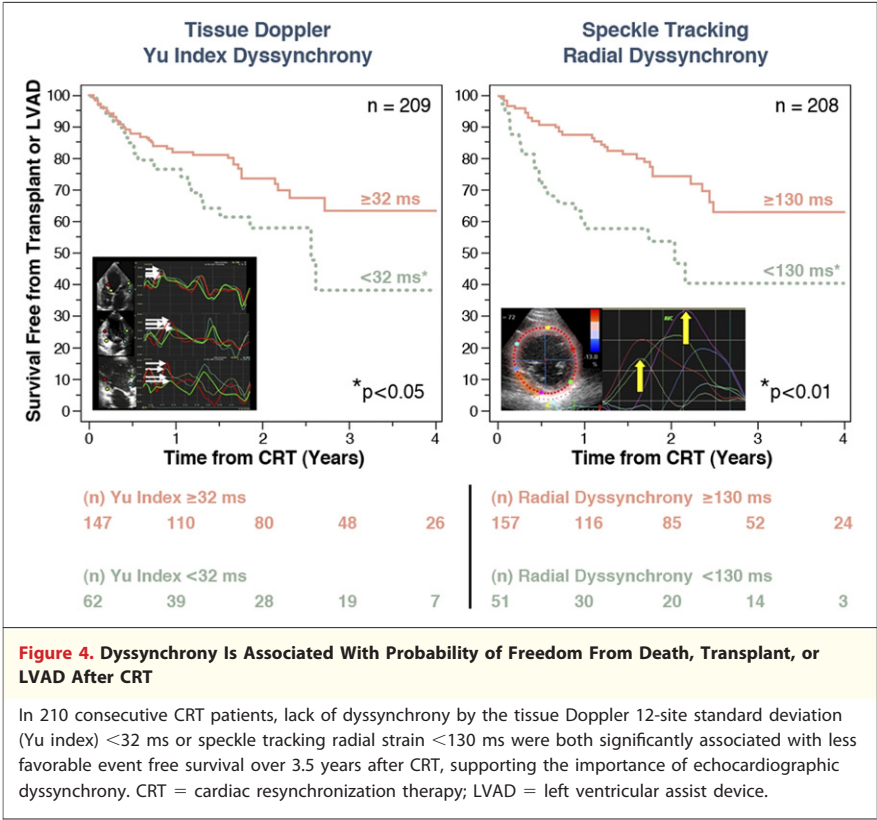
Figure 3. Mortality of Patients Assigned to CRT or Control Group in CARE-HF

The mortality of patients assigned to cardiac resynchronization therapy (CRT) or to the control group in the CARE-HF (Cardiac Resynchronization–Heart Failure) study. Note the disparity between outcome and response. NT-proBNP = N-terminal pro-B-type natriuretic peptide; RR = relative risk reduction.

while. The significant costs associated with unnecessary CRT implantations are even more important in the current climate of global economic concerns. The rationale to avoid the risk of procedural complications and cost savings by identifying patients who are nonresponders prospectively is an attractive notion that is worthy of further exploration.

The dyssynchrony hypothesis states that abnormalities of regional mechanical activation (i.e., dyssynchrony)—in particular LV septal-free wall activation delay—are related to biological derangements that are improved by CRT (31). Widening of electrocardiographic QRS complex is thought to be a marker for mechanical dyssynchrony, but direct measures of dyssynchrony by cardiac imaging have not been adequately tested in a large-scale randomized clinical trial. For example, although enrollment in the CARE-HF trial required patients with lesser degrees of QRS widening between 120 ms and 149 ms to meet 2 of 3 additional criteria for dyssynchrony (an aortic pre-ejection delay >140 ms, an interventricular mechanical delay >40 ms, or delayed activation of the posterolateral LV wall), this study did not test the

predictive value of these dyssynchrony indices in a randomized manner. Despite the absence of existing data from randomized trials, there is an abundance of peer-reviewed publications that have shown that patients who lack mechanical dyssynchrony fail to respond to CRT as favorably as do patients with evidence of it (17). In addition to M-mode, tissue Doppler, and routine pulsed Doppler (17,32), a number of new technologies have been added, including 3-dimensional echocardiography and speckle tracking (33–35). A setback to the utilization of echocardiographic means to measure dyssynchrony and potentially predict patient nonresponders was the PROSPECT study (36). This multicenter observational study from Europe, the U.S., and Hong Kong demonstrated that several echocardiographic dyssynchrony measures were indeed significantly predictive of response to CRT; however, technical factors with acquisition and analysis led to problems with yield and variability. This ambitious study was flawed because of confounding variables of different equipment and software, multiple echocardiography core laboratories, and an overly



complex study design; and many consider that this is not the final word in echocardiographic dyssynchrony analysis (37). Regardless, the current consensus is that echocardiographic means should not be used to select patients for CRT if they meet the routine clinical selection criteria, although a report from the American Society of Echocardiography endorsed by the Heart Rhythm Society has proposed that echocardiographic dyssynchrony may be used as an adjunct to other criteria for patients who are borderline candidates (17). Despite their limitations, tissue Doppler longitudinal velocities, pulsed Doppler interventricular mechanical delay, and speckle tracking are among the most promising current methods to assess dyssynchrony. Recent preliminary data indicate that the tissue Doppler 12-site standard deviation (Yu index) and speckle tracking radial strain were associated with the important outcome

of survival free from transplant or mechanical support (38) (Fig. 4). Future evolving approaches include 3-dimensional echocardiography (including 3-dimensional speckle tracking) and cardiac magnetic resonance (39); further work is needed to determine their utility for widespread clinical applications.

Data continue to emerge that scar burden is an important determinant of response to CRT (40,41), and emphasize that the presence or absence of mechanical dyssynchrony to determine response to CRT is clearly an oversimplification of reality. Because randomized clinical trials have enrolled patients who have ischemic cardiomyopathy along with those who have nonischemic disease, the role of scar has been explored only as part of subset analysis. The majority of findings have indicated that the presence of coronary artery disease, in particular patients who have a high scar burden, appear to have a less favorable prognosis than do patients

who have nonischemic cardiomyopathy after CRT. This intriguing factor, which is complexly related to the progressive natural history of coronary artery disease, the relationship with lead position and scar, and the overall scar burden appears to have a powerful impact on patient outcome after CRT (42). A reasonable goal would be to identify specific criteria where magnitude of scar burden may reliably predict nonresponse to CRT. The effects of scar burden may be even more important than dyssynchrony, although this needs to be tested prospectively.

Much attention has been focused on the importance of LV lead positioning to achieve optional resynchronization and response to CRT. Several studies have suggested that LV functional improvement may be enhanced by LV lead positioning at the site of latest mechanical activation (35,42–45). There is physiological evidence that electrically stimulating the regional site of latest activation will result in more effective resynchronization, in particular if that site is free from significant scar. However, precise localization of LV lead position may be less important in patients with a large “sweet spot” for electrical stimulation (46). An optimal imaging method to reliably map timing of regional activation has not yet been described because of technical complexities (47). Furthermore, limitations remain with accessibility for stable lead positioning despite optional mechanical mapping because of variability in coronary venous anatomy. Prospective mapping of mechanical activation to advise the electrophysiologist to target remains a potential goal to refine patient selection for optimal delivery of CRT.

The presence of heart failure that is too advanced to respond to CRT is an important consideration that may in part be addressed by the degree of QRS widening (48). In addition to

lack of dyssynchrony, high scar burden, and improper lead positioning, there appear to be factors that have not yet been defined that may predict nonresponse to CRT. Subsets of patients exist with heart failure that continues to progress despite all attempts at pharmacological and device therapy. These unfortunate patients often require mechanical circulatory support or heart transplantation as their only therapeutic options. Although several attempts have been made to identify these patients who are on an irreversible path of disease progression who would not be appropriate candidates for CRT, no reliable indicator has yet been established. Novel biological markers or measures by advances in cardiac imaging may help identify these patients with the very worst prognosis.

The next frontier worthy of further exploration is the application of CRT to patients with heart failure and mechanical dyssynchrony, despite having a narrower QRS complex. Since a dissociation of QRS width and mechanical dyssynchrony has been described, investigators have been motivated to extend the benefits of CRT to a larger group of heart failure patients who may benefit. This shifts the importance of assessing dyssynchrony by imaging from an adjunct to refine patient selection in patients with wide QRS, to a requirement in patients with narrow QRS.

Two single-center nonrandomized studies introduced the concept of bene-

fit to CRT in narrow QRS interval heart failure patients who have mechanical dyssynchrony identified by tissue Doppler imaging (49,50). The first and only randomized trial of CRT in heart failure patients with narrow QRS interval (<130 ms) was known as the RethinQ (Resynchronization Therapy in Narrow QRS) study (51). The vast majority of these patients ($>90\%$) were selected by tissue Doppler septal-to-lateral or septal-to-posterior wall peak longitudinal velocity delays of ≥ 65 ms. This study was reported overall as a negative in part because the primary end point of improvement in peak myocardial oxygen consumption at 6 months was not different in treatment and control groups. However, several elements of this trial were encouraging, including a significant improvements in New York Heart Association functional class in 54% of CRT-treated patients versus 29% of control patients overall ($p < 0.006$) and significant improvements in 6-min walk distance in CRT-treated patients with nonischemic disease compared with controls. Furthermore, there were less heart-failure events requiring intravenous therapy in the CRT group: 24 events compared with 41 events in the control group. Although this observation did not reach significance, it was clearly hypothesis generating that mechanical dyssynchrony perhaps may identify patients with narrow QRS who may benefit from CRT. Why did the RethinQ study fail? Possibilities are that the primary end point of peak myocar-

dial oxygen consumption had too much variability in this population, too small of a sample size, too short of a follow-up period, or utilization of the wrong dyssynchrony index or cutoff. Although the possibility exists that CRT will not benefit patients with a narrow QRS width despite overcoming all of the above factors, effort is being invested in future investigations.

Utilization of cardiac imaging to improve patient selection and outcome for CRT is a worthy goal. Identifying the wide QRS interval patient who has little to no chance of response to CRT will improve patient care by decreasing the risk of unnecessary procedures and through appropriate resource utilization. Further benefit will result from increased knowledge in how to measure mechanical dyssynchrony and what it means, scar burden, and map mechanical activation for lead positioning. Finally, cardiac imaging, in particular echocardiography, has the potential to play a critical role in the selection of heart failure patients with narrow QRS interval who may benefit from CRT and improve their long-term outcomes. Future randomized clinical trials are needed to test this intriguing hypothesis.

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